Application P 98 03034 filed 29 December 1998 has been made of record in Applicants' PCT/HU99/00102 filed 23 December 1999 of which the instant application is the U.S. National Phase. The Examiner has already acknowledged Applicants' perfected right of priority.

Applicants are submitting a substitute specification to provide a clean copy of the application There are several changes in the specification appearing on pages 1 through 4. A copy of the marked up original specification has been provided. No new matter has been inserted into the specification.

Claim 10, line 3 has been amended to delete the words "acid addition" since the salts of 1-(aminomethyl)-cyclohexyl-acetic acid are not acid addition salts. See original claim 1. Applicants have added new claim 18 antecedent basis for which may be found in the specification on page 4, lines 22 to 26. Thus claims 10 through 18 are now in the application and are presented for examination.

Applicants appreciate the Examiner's indication that the application contains allowable subject matter.

The Examiner has rejected the independent process of preparation claim 10 under 35 USC 112, first paragraph, on the grounds that the claim is not supported by an enabling disclosure. Specifically the Examiner is troubled by the broad term in line 10 "hydrogenation catalyst" which the Examiner considers to be too broad since the only hydrogenation catalyst that Applicants have successfully used to hydrogenate a compound of the Formula (II) to

form a compound of the Formula (III) is palladium on activated carbon. The Examiner is aware that Applicants name other hydrogenation catalysts on page 4, lines 22 through 26. There Applicants mention "rare metal catalysts, e.g. rhodium or palladium, Raney nickel or cobalt catalysts..." The Examiner argues, however, that catalysis is an unpredictable art and the only hydrogenation catalyst that Applicants have shown to successfully hydrogenate a compound of the Formula (II) is palladium-on-carbon.

Applicants do not agree that catalytic hydrogenation is so unpredictable. Catalytic hydrogenation of nitro compounds to obtain amino compounds has been known to those "skilled in the art" for many years and such a hydrogenation step is a common process used in organic synthesis. In such a process several types of hydrogenation catalysts can be used interchangeably so that one hydrogenation catalyst can be routinely substituted for another to obtain the same product with perhaps only some difference in product yield or purity. Therefore in principle it is highly predictable that the well-known and commonly used catalysts may be substituted for one another in hydrogenation of a nitro compound to form the corresponding amino compound. One "skilled in the art" knowing that the use of Raney nickel to catalyze the hydrogenation of a nitro compound to form the amino compound would also work if palladium were substituted as hydrogenation catalyst for the Raney nickel.

Applicants note that claim 1 of U.S. Patent 5,091,567 to GEIBEL et al which is equivalent to EP 0414 274 cited in the

European Search Report and in the background portion of the present application defines the hydrogenation catalyst as "a noble metal catalyst" even though the only noble catalyst that is exemplified (see Examples 8 and 15) or even named (see col. 5, lines 46 and 47) in the reference is palladium-on-carbon.

Furthermore Applicants have added new dependent claim 18 which limits the hydrogenation catalyst to "a rare metal, Raney nickel or cobalt catalyst " as described in the present application on page 4, lines 22 to 26. By "rare metal" what is meant is a platinum group metal such as rhodium or palladium (see line 24 of page 4 of the specification) and not a rare earth. Claim 18 is especially believed to be allowable since it is limited to a narrower group of very well known hydrogenation catalysts that have been used for many years to successfully hydrogenate a nitro compound to form the corresponding amino compound.

The Examiner has made an argument that case law written by the U.S. Patent and Trademark Office Board of Appeals and by the Courts supports the Examiner's argument that the definition of the hydrogenation catalyst should be limited because catalysis is an unpredictable art and more than routine experimentation would be needed to determine which hydrogenation catalysts known in the art would actually work to reduce the present Formula (II) compound to form the Formula (I) compound and which would not work. The Examiner appears to be citing In re Wands, 8 USPQ 2d 1400 (CAFC 1988) and Ex parte Forman, et al, 230 USPQ 546 (PTO Bd. App. 1986) when he mentions "Forman factors or Wands factors" on page 2 of the

official action. Applicants do not believe that either of these decisions is relevant to the present case. In Forman the Examiner did raise the issues of enablement and undue experimentation under 35 USC 112, first paragraph, just as in the present case, but the facts are so far removed from the present case, that the decision is not applicable. The Forman decision does not relate to catalytic hydrogenation, but relates to a new vaccine for immunizing a patient against enteric diseases. with a genetic hybrid bacterium as the active ingredient. In Forman the questions of enablement and undue experimentation relate to how the active ingredient in the vaccine is prepared. The Examiner argued that one of the starting materials, a particular S. typhi mutant strain was not commercially available and in the absence of a permanent deposit by the applicant, one "skilled in the art" could not make the active ingredient for the vaccine without the need to carry out undue experimentation. The Examiner also argued that the process used to prepare the active ingredient in Forman, known as hyperconjugation, is a new process and it is unpredictable as to the results that will be obtained. The fact that the Patent and Trademark Office Board of Appeals agreed with the examiner in Forman that the application did not contain a sufficient disclosure to enable the practice of the invention in no way provides any basis for the Examiner's rejection of the claims in the present application for lack of enablement. While there may be some unpredictability associated with catalysis, catalytic hydrogenation is an old, well-known process unlike hyperconjugation and so Forman should not

apply. The broad definition of the hydrogenation catalyst as a noble metal found in the independent claim of U.S. Patent 5,091,567 supports our argument that catalytic hydrogenation is not the equivalent of hyperconjugation in terms of predictability.

The Wands decision is also a decision in the biotech field that does not relate to catalytic hydrogenation. The Wands decision relates to an immunoassay method for the hepatitis B surface antigen (HbsAg) using high affinity monoclonal antibodies of the IgM isotype and that these particular monoclonal antibodies detected the antigen with surprisingly high sensitivity and specificity. The Examiner argued that the specification in Wands was not enabling because (1) there was no deposit in a permanent depository of the hybridomas needed to secrete the monoclonal antibodies and (2) there was not enough disclosure of how to produce the high affinity monoclonal antibodies of the IgM isotype without the need to conduct undue experimentation since the data in the Wands application showed that the process to produce such monoclonal antibodies was unpredictable and unreliable and would require undue experimentation of one "skilled in the art" trying to practice the Wands invention. Specifically only a fraction of the hybridomas produced by Wands in the fusion process produced monoclonal antibodies that were effective in binding to the HbsAg. Thus the examiner and the Board of Appeals considered the Wands process to be too unpredictable and required an undue amount of experimentation to successfully practice the invention. Furthermore the examiner and the Board of Appeals concluded that in

the absence of a deposit of the viable hybridomas in a permanent depository, the enablement requirement of the patent statute was not satisfied.

The Court ruled that none of the arguments by the Examiner or the Board was sustainable and reversed the rejection of the claims as based upon an inadequate disclosure. The Court made it clear that there is no requirement of depositing the hybridomas in a permanent depository when the specification itself would enable one "skilled in the art" to prepare without the need to conduct undue experimentation hybridomas that will secrete the monoclonal antibodies. Furthermore the fact that one would have to screen hybridomas to find out which ones produce viable monoclonals does not amount to "undue experimentation" even if the majority of the hybridomas do not produce the viable monoclonals. Such experimentation would be expected. Thus the Court ruled in favor of the applicant and against the Patent and Trademark Office. Thus the Wands decision in no way supports the Examiner's argument that the present application is not enabling to support the catalytic hydrogenation as presently claimed.

In fact Wands is actually supportive of the Applicants' position since Wands makes it clear that a certain amount of experimentation is entirely acceptable in practicing the invention disclosed in a U.S. Patent. In the present case one "skilled in the art" could pick and choose among conventional hydrogenation catalysts such as a platinum group metal or Raney nickel and

determine which ones catalyze the hydrogenation of the Formula (II) compound the best.

The Examiner has also cited Ex parte Sizto, 9 USPQ 2d 2081 (Bd. App. 1988) to provide support for his argument that catalysis is an unpredictable art. In Sizto an analytical method is claimed using a catalyst which facilitates a reaction between an analyte (unknown) and a solute (reagent). Such a reaction permits the determination of the presence or absence of the analyte in a given sample. The process claims a "catalyst" without any further qualification whatsoever even though the only catalyst actually exemplified in but one example is an enzyme. The examiner and the Board of Appeals both agreed that the term catalyst was too broad because there was no limitation whatsoever on the identity or the function of the catalyst. The Board specifically pointed out that there are many catalysts that are not enzymes and there is no evidence that any catalyst that is not an enzyme will work in the Sizto method. Other catalysts that were originally contemplated by Sizto included metal complexes and electron transfer agents which are far removed from enzymes. Furthermore the Board noted that one of the other reagents in the analytical method had to be an enzyme even where the applicant planned to use a non-enzyme catalyst. The Board indicated that it was highly speculative that such a method would work where the catalyst was anything but an enzyme and affirmed the rejection.

The present process is directed to the catalytic hydrogenation of a nitro compound of the Formula (II) using a hydrogenation catalyst. Hydrogenation catalysts are typically metals and do not encompass enzymes or the other diverse kinds of catalysts mentioned in Sizto. The holding in Sizto is not that catalysis in general is unpredictable, but that the kind of catalysis called for by the analytical method of Sizto is unpredictable if catalysts other than enzymes are contemplated. Thus Sizto provides no basis for the Examiner's requirement that Applicants limit the catalyst in their hydrogenation process to palladium-on-carbon.

The Examiner has also cited In re Armbruster, 185 USPQ 152 (CCPA 1975) which is directed to a process for hydrolyzing starch to obtain a starch product having a dextrose equivalent (D.E.) less than 15 using bacterial alpha-amylase to increase the D.E. The application also disclosed that the process was useful to obtain a starch hydrolysate with a D.E. of 5 to 15. The Examiner took the range of 5 to 15 to mean that a starch hydrolysate with a D.E. less than 5 would not be operative. The issue here was not the scope of the kinds of enzymes used to facilitate the hydrolysis, but whether the applicant really established that his process could obtain the starch hydrolysate product having a D.E. less than 15, including a D.E. below 5 is still a useful product. The Court held that the Examiner had insufficient evidence to establish that a starch hydrolysate with a D.E. less than 5 would be inoperative and only made such a speculation based upon the lower end of this disclosed range.

There is no similarity whatsoever between the facts in Armbruster and those in the present case since the process in the present case includes no range where one portion of that range arguably could encompass inoperative subject matter. Furthermore the Court in Armbruster ruled in favor of the applicant and against the Patent and Trademark Office on the issue of enablement and so the decision actually helps the present Applicant more than it helps the Examiner's position. Nothing in the Armbruster decision supports any argument that the claims in the present case with the broadly defined hydrogenation catalyst cover catalysts that will not work and leave the Examiner to prove that any such catalyst within the scope of the presently claimed invention will not work.

Finally In re Angstadt and Griffin, 190 USPQ 1976 (CCPA 1976) has been cited for its disclosure that catalytic processes are unpredictable and that the scope of the enablement varies inversely with the degree of unpredictability. The Examiner and the Board of Appeals questioned whether the claimed process which was a process to catalytically oxidize secondary or tertiary alkyl aromatic hydrocarbons to form a reaction mixture containing the corresponding hydroperoxide using an organometallic complex as the catalyst. The application also stated that some of the catalyst complexes will not effectively facilitate oxidation of the starting materials. The Court reversed the Examiner and the Board stating that the evidence as a whole showed that the process was operative notwithstanding that some particular catalysts may be inoperative. The Court held essentially that some experimentation by one

"skilled in the art" seeking to work the patent to find the best catalysts for the process does not amount to "undue experimentation" and is permissible under the patent statute. Thus this decision is supportive of the right of the present Applicants to obtain a patent with the broad definition of the hydrogenation catalyst.

Furthermore Applicants have carried out additional examples showing catalystic hydrogenation of the compound of the Formula (II) where R is hydrogen to yield 1-(aminomethyl)cyclohexyl acetic acid of the Formula (I). Instead of palladium, the catalysts tested were Raney nickel and Adams catalyst. The examples are as follows:

Example 3

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To the solution Raney Ni catalyst (1 g) was added and was hydrogenated at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To a residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

Yield: 2.1 g (39.6 %)

Melting point: 165-9°C

Example 4

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To a solution Adam's catalyst (0.07 g) was added and was hydrogenated at atmospheric

pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To the residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

The examples show clearly that the hydrogenation process can be carried out with other types of catalysts.

Applicants will make these additional examples of record in a Declaration Under 37 CFR 1.132. Accordingly no rejection of any claim should be maintained under 35 USC 112, first paragraph, for lack of an enabling disclosure.

The Examiner has incorrectly rejected intermediate compound claims 14 through 17 as dependent upon a rejected base claim. This is incorrect because claim 14 is an independent claim. Applicants request that the compound claims be considered allowable as well. The Examiner has provided no reason and has cited no prior art to provide any basis to reject these intermediate compound claims as obvious under 35 USC 103.

The references cited by the Examiner has been cited merely to show the state of the art and have not been applied against any of the claims as the basis for an anticipation rejection or an obviousness rejection.

Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

Applicants enclose a petition to obtain a one month extension of the term for response and authorization

Respectfully submitted,
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Enc: Substitute Specification
Marked up version of
Original Specification
Petition for Extension
PTO 2038 Charge Form

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